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Re-evaluation Decision

RVD2014-01

Propoxur

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Table of Contents

Re-evaluation Decision for Propoxur	1
What Does Health Canada Consider When Making a Re-evaluation Decision?	2
What is Propoxur?	2
Health Considerations	3
Environmental Considerations	7
Value Considerations	7
Measures to Minimize Risk	8
What Additional Scientific Information is Being Requested?	9
Other Information	9
List of Abbreviations	11
Appendix I Comments and Responses	13
1.0 Comments Relating to Health	13
1.1 Comment – Cancer risk assessment	13
1.2 Comment – Pet transfer calculation	14
1.3 Comment – Pet collar transferable residue study	14
1.4 Comment – Indoor crack and crevice uses	14
Appendix II Revised Toxicology Assessment for Propoxur	15
Table 1 Toxicity Profile of Propoxur	20
Table 2 Toxicological Endpoints for Use in Health Risk Assessment for Propoxur	21
Appendix III Revised Occupational and Residential Exposure Assessment	23
Table 1 Summary of Use Scenarios and Risks of Concern	24
Table 2 Short-term Occupational Mixer, Loader, Applicator Dermal and Inhalation Exposure Estimates and Margins of Exposure	25
Table 3 Dermal Exposure and Cancer Risk Estimates for Commercial Mixer, Loader, Applicators	26
Table 4 Inhalation Exposure and Cancer Risk Estimates for Occupational Mixer, Loader, Applicators	27
Table 5 Short-term Residential Applicator Dermal and Inhalation Exposure Estimates and Margins of Exposure	27
Table 6 Dermal Exposure and Cancer Risk Estimates for Residential Applicators	28
Table 7 Inhalation Exposure and Cancer Risk Estimates for Residential Applicators	29
Table 8 Postapplication Dermal Exposure Estimates and MOEs from Indoor Application	29
Table 9 Postapplication Dermal Exposure Estimates and MOEs from Pet Collar Application Using Chemical Specific Data	30
Table 10 Postapplication Inhalation Exposure Estimates and MOEs from Indoor Surface Directed Application	31
Table 11 Incidental Oral Exposure Estimates and MOEs for Hand-to-Mouth Transfer to Children	31
Table 12 Incidental Oral Exposure Estimates and MOEs for Object-to-Mouth Transfer to Children	32
Table 13 Dermal Exposure and Cancer Risk Estimates for Postapplication Residential Exposure to Indoor Surfaces	32

Table 14	Dermal Exposure and Cancer Risk Estimates for Postapplication Exposure to Pet Collars Using Chemical Specific Data	33
Table 15	Inhalation Exposure and Cancer Risk Estimates for Indoor Residential Postapplication Exposure Following Surface Directed Application	33
Table 16	Incidental Oral Exposure and Cancer Risks for Hand-to-Mouth Transfer to Children.....	34
Table 17	Incidental Oral Exposure and Cancer Risks for Object-to-Mouth Transfer to Children.....	34
Appendix IV	Revised Dietary Exposure Assessment	35
Table 1	Dietary Exposure and Risk Estimates for Propoxur	35
Appendix V	Label Amendments for Products Containing Propoxur	37
References.....		41

Re-evaluation Decision for Propoxur

After a thorough re-evaluation of the insecticide propoxur, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is proposing continued registration for the sale and use of some propoxur uses in Canada and the phase-out of uses with risk concerns.

An evaluation of available scientific information found that under the revised conditions of use, some uses of products containing propoxur have value and do not present unacceptable risks to human health or to the environment. These uses include indoor crack and crevice applications of Commercial class products in commercial areas and outdoor uses of Domestic and Commercial class products, as well as bait trays. As a condition of continued registration of these uses, new risk-reduction measures are to be implemented.

Certain uses of propoxur are to be phased out because either registrants do not support continued registration or a human health risk of concern has been identified. These are: use to control biting flies including mosquitoes, black flies, gnats, sandflies and punkies, use in pet collars, all indoor uses of Domestic class products except bait trays, and indoor uses of Commercial class products in residential areas.

The regulatory approach regarding the re-evaluation of propoxur was first presented in Proposed Re-evaluation Decision PRVD2011-09, *Propoxur*, a consultation document.¹ This Re-evaluation Decision Document² describes this stage of the PMRA's regulatory process concerning the re-evaluation of propoxur and summarizes the Agency's decision, the reasons for it and, in Appendix I, a summary of comments received during the consultation process and the PMRA's response to these comments. Additional data was received during the consultation process and some assessments were revised as a result. These revised assessments are presented in appendices II and III. This decision is consistent with the proposed re-evaluation decision stated in PRVD2011-09. To comply with this decision, registrants of propoxur products will be informed of the specific requirements affecting their product registration(s) and of the regulatory options available to them.

For more details on the information presented in this Re-evaluation Decision, please refer to the related Science Evaluation section of the previously published consultation document on propoxur (PRVD2011-09).

¹ "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

² "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

What Does Health Canada Consider When Making a Re-evaluation Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the pesticide under its conditions or proposed conditions of registration.³ The *Pest Control Products Act* also requires that products have value⁴ when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies risk assessment methods as well as policies that are rigorous and modern. These methods consider the unique characteristics of sensitive subpopulations in both humans (for example, children) and organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management section of the Health Canada's website at www.healthcanada.gc.ca/pmra.

What is Propoxur?

Propoxur is a non-systemic carbamate insecticide that is currently registered for use to control a broad range of insect and arthropod pests on a wide variety of sites including: structures (indoors and outdoors), transportation vehicles (for example, boats, ships, trucks, trains), on companion animals, in human habitat and recreational areas (for biting fly and mosquito control) and in residential outdoor areas.

The currently registered labels indicate that propoxur is applied by both ground and aerial means, using mist blowers, foggers and ultra-low volume application equipment to control mosquitoes and other biting flies. Cats and dogs are treated using slow release pet collars. Propoxur is also applied to other sites using pressurized spray cans, hand held and backpack sprayers, and paste applicators by professional applicators and casual users such as home owners.

³ "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

⁴ "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact".

Health Considerations

Can Approved Uses of Propoxur Affect Human Health?

With the exception of bait trays, additional risk-reduction measures are required for propoxur. Propoxur is unlikely to affect your health when used according to the revised conditions and label directions.

Potential exposure to propoxur may occur through the diet, when handling and applying the product, or when entering or contacting treated sites. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose at which no effects are observed. In laboratory animals, a single high dose of propoxur caused high oral toxicity, low dermal toxicity, and slight inhalation toxicity. Propoxur is a mild eye irritant, and is not a skin irritant or sensitizer. Acute overexposure to propoxur can inhibit cholinesterase, an enzyme necessary for normal functioning of the nervous system. Clinical signs typical of cholinesterase inhibition were observed by all routes of exposure in acute toxicity studies and included tremors, shortness of breath, salivation, and apathy. The onset of neurotoxicity was rapid but the effects were transient.

Health effects in animals given daily oral doses of propoxur over longer periods of time included cholinesterase inhibition and liver toxicity. No treatment-related effects, including effects on cholinesterase activity, were observed in rabbits exposed to repeated dermal applications of propoxur at the limit dose. Cholinesterase inhibition was the most sensitive endpoint in repeated dose inhalation studies in rats. The severity of neurotoxicity increased with repeated inhalation, but not repeated oral dosing.

There was evidence of urinary bladder and liver carcinogenicity in rats after long-term oral or inhalation exposure. The genotoxicity data for propoxur yielded both positive and negative results. Supplementary evidence in public literature suggests that propoxur can suppress the immune system.

There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies. In reproductive studies, maternal cholinesterase activity was the most sensitive endpoint, although cholinesterase inhibition was not measured in offspring. When pregnant animals were orally exposed to propoxur, effects on the developing fetus were only observed at doses that caused death in the mother. Young juvenile rats demonstrated sensitivity to cholinesterase inhibition when compared to adult animals in single dose oral studies.

Implementation of the risk reduction measures will minimize human exposure and ensure any exposure is well below the lowest dose at which the above mentioned effects occurred in animal tests.

Residues in Food and Drinking Water

Dietary risks from food and drinking water are not of concern.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and drinking water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (acceptable daily intake). An acceptable daily intake is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Exposure for all Canadians through drinking water is minimal since propoxur is primarily registered for indoor, non-dietary use. The only registrant-supported outdoor uses are structural applications to the perimeter of buildings. This indicates that the exposure of environmental compartments to propoxur, such as surface, ground and drinking water will be minimal.

Although propoxur is not applied directly to crops, human dietary exposure to propoxur was estimated from residues in food commodities, resulting from exposure in treated areas (for example, food handling establishments). This exposure to propoxur represents 72% of the acute reference dose and 33% of the chronic reference dose for the most highly exposed subpopulation of children aged 1–2 years old, and is not of concern (refer to Appendix IV). The lifetime cancer risk is 2×10^{-7} for the general population and is not of concern (refer to Appendix IV). A lifetime cancer risk that is at or below 1×10^{-6} (one in a million) usually does not indicate a risk concern for the general population when exposure occurs through pesticide residues in/on food and drinking water, and to otherwise unintentionally exposed persons.

Overall, the PMRA has concluded that risks to health from dietary (food and drinking water) exposure to propoxur are not of concern.

Exposure in Residential and Other Non-Occupational Environments

Propoxur is currently used in and around homes, either through application of domestic-class products by residential applicators or by application of commercial-class products by professional pest control operators. Indoor applications can be crack and crevice treatment, perimeter treatment, or spot surface treatment. Propoxur is also used in residential bait trays and in pet collars.

Residential handler non-cancer and cancer risks are not of concern.

For residential applicators applying domestic-class products, including pet collars and bait trays, the calculated dermal and inhalation margins of exposure (MOEs) are greater than the target MOE for all residential applicator exposure scenarios and are not of concern. The calculated dermal and inhalation cancer risks are below 1×10^{-6} and are also not of concern.

For postapplication exposure following indoor application of propoxur, non-cancer risks of concern were identified for children. Cancer risks were identified for most uses. Therefore, risk mitigation is required for indoor application.

For indoor postapplication exposure, the calculated dermal and inhalation MOEs for adults and youths are greater than the target MOE and are not of concern. The calculated inhalation and incidental oral treated surface-to-hand-to-mouth MOEs do not meet the target MOE for children and are of concern.

Calculated dermal cancer risks are above 1×10^{-6} and are of concern for residential postapplication exposure scenarios involving perimeter treatment. Inhalation cancer risks are above 1×10^{-6} and are of concern for all surface treated residential postapplication exposure scenarios. Dermal cancer risks are below 1×10^{-6} and are not of concern for residential postapplication scenarios involving crack and crevice treatment. Incidental oral cancer risks are below 1×10^{-6} and are not of concern for all residential postapplication scenarios.

To mitigate risk from indoor applications of propoxur, propoxur must not be applied to indoor residential use sites, including homes, hospitals, schools, public buildings, day-care facilities, motels, hotels, passenger areas of trains, buses or airplanes, or other indoor locations where children may be exposed.

For postapplication exposure from use of pet collars containing propoxur, non-cancer risks of concern were identified for children. Therefore, risk mitigation is required.

For exposure to people interacting with pets wearing pet collars, the calculated dermal MOEs for all age groups meet the target MOE and are not of concern. The calculated lifetime cancer risks for pet collars are below 1×10^{-6} when using registrant submitted residue data and are not of concern. The incidental oral MOE for treated pet-to-hand-to-mouth for children does not meet the target MOE and is of concern.

To mitigate the risk to children from pet collar applications of propoxur, all pet collar products containing propoxur will be phased out.

There are no risk concerns for residential bait trays.

Postapplication exposure from use of bait trays was considered to be negligible because the active ingredient is enclosed in a self-contained unit and is not available for exposure.

Outdoor residential non-cancer and cancer risks are not of concern.

Postapplication exposure from outdoor applications of propoxur were considered to be negligible, provided that outdoor applications are not made to vegetation, plants, grass or any area accessible to children.

Outdoor residential crack and crevice, structural and stinging insect nest treatments must be limited to areas not frequented by, or inaccessible to, children and the potential for postapplication exposure is minimal. To minimize potential exposures for outdoor treatments propoxur must be limited to crack and crevice, structural and stinging insect nest treatments and must not be applied to vegetation, plants, grass and/or any area accessible to children.

Occupational Risks from Handling Propoxur

Occupational non-cancer and cancer risks are not of concern, provided that risk mitigation measures are taken.

For commercial applicators or pest control operators (PCOs) applying propoxur products, the calculated dermal and inhalation MOEs exceed the target MOE for almost all scenarios using baseline personal protective equipment and are not of concern.

The calculated dermal and inhalation cancer risks are below 1×10^{-5} for most scenarios using baseline personal protective equipment and are not of concern.

Mechanically-pressurized handgun application of emulsifiable concentrates and solutions are of concern for non-cancer and cancer risks. The MOEs did not meet the target MOE, and the cancer risks were above 1×10^{-5} for mechanically-pressurized handgun. Therefore, mitigation is required for this application equipment.

All possible mitigation measures to reduce occupational exposures from use of mechanically-pressurized handgun equipment including personal protective equipment were considered; however, continued application by this method was still not considered to be acceptable. Product labels will be revised to prohibit application using mechanically-pressurized handgun equipment.

Occupational non-cancer and cancer risks are not of concern for postapplication workers.

For workers entering treated sites, it was assumed that postapplication worker exposure would be similar to or less than people exposed in residential areas. The calculated residential dermal and inhalation MOEs exceed the target MOE for adults and are therefore, not of concern for workers. The calculated residential dermal and inhalation cancer risks are below 1×10^{-5} and are also not of concern for workers.

Clarification of the use instructions on the label is required in order to be consistent with the assumptions used in the exposure assessment and/or to be consistent with the mitigation measures for residential areas. These include limiting applications in indoor non-residential areas to perimeter and crack and crevice application only. Outdoor applications must be limited to crack and crevice, structural and stinging insect nest treatments and must not be applied to vegetation, plants, grass and/or any area accessible to children.

Environmental Considerations

What Happens When Propoxur Is Introduced into the Environment?

Propoxur does not pose a potential risk to terrestrial and aquatic organisms since, based on the use pattern, the environmental exposure is expected to be negligible. Additional risk-reduction measures are not needed.

Propoxur is moderately persistent to persistent with the main route of dissipation being biotransformation in soil. Propoxur is not expected to volatilize significantly. Propoxur is mobile in soil. Therefore, there is a potential for propoxur to move to groundwater and surface water, if propoxur was registered for significant outdoor use. However, according to the use pattern of propoxur, the environmental exposure is expected to be minimal.

Propoxur would pose a risk to terrestrial and aquatic organisms if there was environmental exposure. However, the use pattern indicates that potential exposure of non-target organisms is expected to be minimal.

Value Considerations

What Is the Value of Propoxur?

Propoxur is registered in Canada for the control of a wide spectrum of pests on a large number of sites.

In Canada, propoxur is registered to control a wide range of insect and arthropod pests such as: ants, beetles, cockroaches, flies, fleas, millipedes, mites, mosquitoes, spiders, sow bugs, ticks, wasps, and other insect pests on the following sites:

- on and in structures (commercial, industrial, institutional and residential);
- in transportation vehicles such as ships, trains, trucks, etc.;
- in outdoor residential sites;
- on companion animals (cats and dogs); and
- in human habitats and recreational sites to control black flies and mosquitoes.

Excluding fumigants, there are a few alternative active ingredients to propoxur registered in Canada with a broad spectrum of control of structural pests. Such active ingredients include silicon dioxide (diatomaceous earth and silica aerogel), boric acid and synthetic pyrethroids.

Propoxur is important for the purpose of resistance management of structural insect pests.

Propoxur's broad spectrum of control of insects and arthropods makes it valuable as an alternative active ingredient to the synthetic pyrethroids (resistance mode of action (MoA) group 3 insecticides) which are also registered for the control of a wide range of structural pests and account for the majority of products registered in Canada for this use.

Propoxur is a MoA group 1A insecticide. In recent years, the registrations of several carbamate and organophosphate insecticides (MoA group 1A and 1B insecticides, respectively) that were used within structures have been discontinued (for example, bendiocarb, chlorpyrifos, diazinon) or their use patterns have been amended, limiting their use to specific sites or to specific application methods (for example, dichlorvos, propetamphos). This limits the availability of active ingredients from MoA groups 1A and 1B to rotate with the synthetic pyrethroids (MoA group 3 insecticides) leading to the potential for limited resistance management options.

Propoxur is characterized as providing rapid knockdown and has a long residual action.

Knockdown, which is characterized as an insect's inability to walk or fly, is rapid with propoxur. Residual action allows propoxur to continue to kill insect pests even after the spray has dried. These traits are important for the control of public health pests such as mosquitoes and cockroaches where immediate and prolonged reduction of a pest population is required.

Alternative active ingredients are available for mosquito control and the pet collar uses of propoxur.

Mosquito control includes the use of pesticides to control the larval and adult stages. Alternative active ingredients to propoxur are available in Canada for the control of mosquito larvae and adults.

Alternative active ingredients to propoxur are available in Canada for the control of fleas and ticks on cats and dogs. These include active ingredients formulated into pet collars and shampoos. Veterinary drugs are also available for control of fleas and ticks on dogs and fleas on cats.

Measures to Minimize Risk

As a result of the revised human health risk assessment, for which further data and the most current exposure methodology was used, there continues to be a high level of concern for pet collar and indoor products containing propoxur applied to residential areas. All pet collar, indoor domestic-class products (except bait trays), and application of commercial-class products in indoor residential areas will be phased out for propoxur as additional mitigation measures are not feasible, and based on available scientific information, these uses do not meet Health Canada's current standards for human health protection and pose unacceptable risks to human health.

Registered pesticide product labels include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions are required by law to be followed.

As a result of the re-evaluation of propoxur, the PMRA is requiring further risk-reduction measures. These measures, in addition to those already identified on existing propoxur product labels, are designed to further protect human health and the environment. The following additional key risk-reduction measures are required.

Additional Key Risk-Reduction Measures

Human Health

- a) To protect commercial mixers, loaders, and applicators: mechanically-pressurized equipment must not be used.
- b) To protect workers entering treated sites: indoor applications to commercial locations will be limited to perimeter application using manually-pressurized handwand, and crack and crevice applications.
- c) To protect residents and residential applicators: all indoor domestic-class products (except bait trays) will be phased out and commercial-class products must not be applied to indoor residential use sites, including homes, schools, public buildings, day care facilities, motels, hotels, passenger areas of trains, buses or airplanes, and other indoor locations where children may be exposed. Specific directions for outdoor domestic-class and commercial-class products are also required.
- d) To protect homeowners/pet owners: all pet collar products will be phased out.

Label amendments to be implemented are found in Appendix V.

What Additional Scientific Information is Being Requested?

No further information is required at this time as a condition of continued registration or to address uncertainties in the risk assessment.

Other Information

Any person may file a notice of objection⁵ based on scientific grounds regarding this decision on propoxur within 60 days from the date of publication of this Re-evaluation Decision Document. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of Health Canada's website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

⁵ As per subsection 35(1) of the *Pest Control Products Act*.

List of Abbreviations

ADD	absorbed daily dose
ADI	acceptable daily intake
a.i.	active ingredient
ARfD	acute reference dose
ARI	aggregate risk index
ATPD	area treated per day
BChE	brain cholinesterase
BMD	benchmark dose
BMD _X	BMD response rate of X%
BMDL _X	BMD at the 95% lower bounds of the response rate of X%
bw	body weight
CAF	composite assessment factor
CCA	Comparative Cholinesterase Assay
ChE	cholinesterase
DA	dermal absorption
EC	emulsifiable concentrate
GLP	Good Laboratory Practices
hr	hour
kg	kilogram(s)
LADD	lifetime average daily dose
LOAEL	lowest observed adverse effect level
m ³	metre(s) cubed
mg	milligram(s)
MLA	mixer, loader, applicator
MoA	mode of action
MOE	margin of exposure
NA	not applicable
NOAEL	no observed adverse effect level
PA	paste
PCO	pest control operator
PCPA	<i>Pest Control Product Act</i>
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PP	pressurized product
PPE	personal protective equipment
PRVD	Proposed Re-evaluation Decision
q ₁ *	cancer potency factor
SN	solution
SOP	Standard Operating Procedure
SR	slow release product
USEPA	United States Environmental Protection Agency

Appendix I Comments and Responses

The PMRA received written comments from the technical registrant relating to the Proposed Re-evaluation Decision PRVD2011-09, *Propoxur*.

1.0 Comments Relating to Health

1.1 Comment – Cancer risk assessment

The registrant commented that the carcinogenic risk assessment for propoxur is overly conservative and unrealistic. They contend that only short term exposure is of concern because actual exposure doses are low and because propoxur metabolism and clearance are rapid. The registrant questioned the differences between the PMRA assessment and the United States Environmental Protection Agency (USEPA) scoping document (2009 Human Health Risk Preliminary Work Plan, PMRA 2045079). In the latter, the USEPA concluded:

- Based on the current knowledge of the non-cancer mode of action for propoxur (i.e., rapid reactivation of the enzyme suppressed by exposure and then recovery), chronic dietary assessments are no longer appropriate for propoxur and are not intended to be conducted during registration review.
- A revised chronic cancer dietary assessment is also not intended to be conducted because the concentrations of exposure which elicited effects in the submitted studies are orders of magnitude greater than what would be expected based on registered use patterns of propoxur.

PMRA Response

In agreement with the USEPA, the PMRA considers that the primary non-cancer mode of action for propoxur is rapid inhibition of acetylcholinesterase, with a rapid reversal when the enzyme is reactivated. For this reason, the chronic daily dietary exposure was considered by the PMRA to reflect a series of acute exposures, with each causing transient inhibition of cholinesterase. As a result, the acceptable daily intake was the same as the acute reference dose.

However, this rapid reversal of inhibition and/or the rapid metabolism and clearance does not counter all adverse effects after long-term exposure to propoxur. If that were the case, no tumors would be observed in long-term studies. In contrast, there were increased urinary bladder tumours observed in both mice and rats in long-term dietary studies, as well as increased hepatocellular tumors in long-term dietary and inhalation studies in male rats. As there are currently no suggested or supported modes of action provided to account for these tumor types, a quantitative risk assessment (i.e., linear low-dose extrapolation) for long-term exposure is required by the PMRA to be protective of any potential cancer health risk. It is agreed that the expected exposure doses are much lower than those tested in the rodent long-term studies. Accordingly, the cancer risk assessments do take into account the expected low doses of human exposure, based on the registered use patterns of propoxur.

1.2 Comment – Pet transfer calculation

The Pet-to-Hand-to-Mouth Transfer calculation for cats uses the same body surface area as that for dogs. The body surface area for a pet is 6,000 cm² (Table 17 in Appendix V of the PRVD). The registrant feels that the surface area for a cat should be less than this. According to the registrant, the USEPA's use of a surface area of 2737 cm² for a house cat is more realistic.

PMRA Response

The residential exposure risk assessment has been revised based on new toxicological endpoints and the 2012 USEPA Residential SOPs, which includes specific body weights for small, medium, and large cats and dogs. See Appendix III for the revised exposure assessment.

1.3 Comment – Pet collar transferable residue study

The registrant is currently conducting a full GLP study monitoring transferable residues over a 28 day period. The in-life phase of this study was started on March 21, 2011. The registrant hopes that PMRA would use data from the full GLP study (available later in 2011) to complete their risk assessment.

PMRA Response

PMRA received this study and has revised the residential exposure risk assessment based on new toxicological endpoints, the 2012 USEPA Residential SOPs and the submitted pet collar transferable residue study. See Appendix III for the revised exposure assessment.

1.4 Comment – Indoor crack and crevice uses

Indoor transferable residue and dissipation data and air monitoring data based on Canadian use patterns and application rate are identified as one of PMRA's data requirements in the PRVD. The registrant believes that the indoor crack and crevice uses should not be cancelled if it can be shown that better data exists or can be generated.

PMRA Response

Cancellation of registration of propoxur for indoor crack and crevice uses was not proposed in the PRVD. Data requirements for these uses were listed in the PRVD as no chemical-specific data was submitted in support of the indoor crack and crevice uses. The data requested was not submitted, therefore the residential exposure risk assessment has been revised based on new toxicological endpoints and the 2012 USEPA Residential SOPs. No further data is required at this time. See Appendix III for the revised exposure assessment.

Appendix II Revised Toxicology Assessment for Propoxur

Toxicological Summary

Pursuant to the toxicological re-evaluation conducted for PRVD 2011-09, the required additional toxicology data were submitted to the PMRA. A newly submitted acute comparative cholinesterase (ChE) assay, in which Sprague Dawley rats were given a single oral (gavage) dose of propoxur in corn oil, was conducted in three parts. There was a time-course acute ChE assay in adult and postnatal day (PND) 11 male rats, a comparative ChE assay (herein referred to as the CCA) with adult and PND 11 rats, and a follow-up acute ChE assay with PND 11 rats using a lower dose-range (herein referred to as the follow-up study). The data were reviewed and relevant parts of the assessment have been revised accordingly.

The time-course acute cholinesterase assay (PMRA #2180504) demonstrated inhibition of cholinesterase in the brain (BChE) and erythrocytes (EChE) at the tested doses of 5 mg/kg bw in adult male rats and 3 mg/kg bw in PND 11 male rats. The time to peak effect was 30 minutes in PND 11 males and 15 minutes in adult males. By 4 hours there was recovery to control levels in adults but only partial recovery in PND 11 pups. Tremors were observed in pups within an hour of dosing but were transient, reversing within 3 hours; no clinical signs were noted in adults. There were no treatment related effects on mortality or brain weight. PND 11 male rats demonstrated greater sensitivity than adult male rats to propoxur, by exhibiting greater EChE and BChE inhibition at the time of peak effect at a lower tested dose, transient clinical signs and slower recovery.

In the CCA (PMRA #2180505), there was significant BChE and EChE inhibition in adults at 2.0 mg/kg bw relative to controls. In comparison, PND 11 pups were affected at 0.3 mg/kg bw. There was pup sensitivity relative to adults to both BChE and EChE inhibition, as well as sensitivity of females relative to males. There were no treatment-related effects on mortality, clinical signs or brain weight.

In the follow-up assay (PMRA #2180506) with PND 11 rats, EChE was inhibited in females pups at 0.1 mg/kg bw, and in male pups at the next highest dose of 0.3 mg/kg bw. BChE inhibition in both sexes occurred at 0.3 mg/kg bw. Females were equally or more sensitive than males to EChE and BChE inhibition.

Benchmark dose (BMD) modelling on the CCA and follow-up study was undertaken by the registrant (PMRA #2180507) and the PMRA (see Table 1). Using the BMD response rates of 10% for BChE and 20% for EChE, the PMRA determined that the brain was the more sensitive compartment for ChE inhibition. The BMD values confirmed the sensitivity of the young. For BChE inhibition, PND 11 pups were 7-14-fold more sensitive than adults using the CCA results and 8-9 fold more sensitive than adults using the follow-up study results. For EChE inhibition, PND 11 pups were 11-14-fold more sensitive than adult animals.

The BMDL₁₀ of 0.054 mg/kg bw, based on BChE inhibition in female PND 11 pups from the follow-up assay, was considered a relevant point of departure for risk assessment as it reflected the most sensitive endpoint and subpopulation in the propoxur database. Although a lower BMDL₁₀ of 0.0232 mg/kg bw was obtained for the PND 11 pups in the CCA, the BMD values for BChE inhibition in PND 11 females were comparable in the CCA and follow-up assay. As more of the doses in the follow-up study were close to the calculated point of departure, the use of this BMDL₁₀ was considered preferable.

The registrant proposed a lower BMDL₁₀ of 0.0285 mg/kg bw based on 10% decreased EChE in PND 11 pups (females and males); however, it should be noted that PMRA uses a benchmark response level of 20% for EChE inhibition. Furthermore, the registrant pooled the genders as they considered that there was no biological reason for there to be a gender difference in ChE inhibition in PND 11 rats. The PMRA's BMD analysis did not suggest that pooling the genders was appropriate for PND 11 pups in the follow-up assay. Notwithstanding these differences, the registrant recognized pup sensitivity based on a 14-fold lower BMD₁₀ in pups (0.0427 mg/kg bw) relative to adults (0.6035 mg/kg bw) for EChE.

A recent publication (PMRA #2228946) reported that in children at 2 years of age, prenatal exposure to propoxur was associated with poorer motor development but unrelated to social and performance development. The study, conducted in Filipino mothers and children, determined fetal exposure to propoxur via gas chromatography/mass spectrometry of meconium samples (further reported in PMRA #2228950). While the conditions of exposure are not likely reflective of Canadian use patterns, the paper is of interest given the identified sensitivity of the young in the toxicology database. Although limited reporting hindered an assessment of the robustness of the study and the reported findings on child neurodevelopment, the PMRA's regulatory response will serve to address any concerns raised by the paper.

Pest Control Products Act Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential pre- and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database, prenatal developmental toxicity studies were available in mice, rats, and rabbits (one study in mice, two studies in rats, three studies in rabbits). There were also two-generation reproduction studies in rats (two studies), as well as an acute comparative cholinesterase assay.

With respect to potential pre- and postnatal toxicity, no evidence of sensitivity of the young was seen in the developmental and reproductive toxicity studies. Maternal cholinesterase inhibition was the most sensitive endpoint in these studies; however, cholinesterase inhibition was not measured in offspring or fetuses. In a 2-generation dietary reproduction study in rats, reproductive effects (decreased pup birth weight, number of implantations per dam and number of pups per dam) and offspring effects (decreased pup weight gain and viability) only occurred at doses causing parental toxicity (cholinesterase inhibition, decreased body weight). In another 2-generation dietary reproduction study in rats with lower dose levels there were no reproductive

or offspring effects. Developmental toxicity studies with propoxur in mice, rats and rabbits provided no evidence of teratogenicity or sensitivity of the fetus with in utero exposure. In mice, fetal mortality and decreased fetal weights were observed but only at doses greater than that which produced maternal mortality. No developmental effects were observed in rats. Developmental effects were only observed in one of three rabbit studies (slight postimplantation loss, a decreased number of pups per dam, slight ossification delay), but this occurred in the presence of maternal mortality.

In the acute oral comparative cholinesterase assay, brain and erythrocyte cholinesterase activities were more inhibited in directly-dosed PND 11 pups than adults. Effects on cholinesterase activity levels in the young were not assessed following in utero or lactational (i.e., "indirect") exposures and therefore, it is not known whether sensitivity is present via these pathways as well. In the absence of these data, it is assumed that fetal or nursing subpopulations would demonstrate at most, a comparable degree of sensitivity to that observed in directly-dosed young animals. The rapid reactivation of cholinesterase activity following inhibition with propoxur, combined with the placental or lactational transfer necessary for the young to be exposed, makes it unlikely that a higher degree of sensitivity would be observed in the indirectly-exposed animals. Therefore, the use of cholinesterase inhibition in the directly-dosed young animal as the point of departure for risk assessment is expected to address concerns relating to indirect exposures.

In summary, with regards to the *Pest Control Products Act* factor, the toxicity data are considered complete and the overall level of concern is low. This conclusion is based on the nature and level of concern for the cholinesterase endpoint and the fact that, for certain risk assessments, the endpoint was established from data on the sensitive subpopulation. Where the endpoint from the sensitive subpopulation was not used in the risk assessment (i.e., the dermal and inhalation assessments), the application of a 10-fold uncertainty factor for database deficiency serves to address residual concerns for potential sensitivity of the young. Accordingly, the *Pest Control Products Act* factor was reduced to 1-fold on the basis of these considerations.

Refer to Table 2 for the updated reference doses.

Determination of Acute Reference Dose (ARfD)

To estimate acute dietary risk for the general population (gen. pop.), the BMDL₁₀ of 0.054 mg/kg bw for brain cholinesterase inhibition was selected from an acute oral comparative cholinesterase follow-up study in PND 11 rats. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The *Pest Control Products Act* factor was reduced to 1-fold, based on the rationale provided in the *Pest Control Products Act* Hazard Characterization section. Therefore, the composite assessment factor (CAF) is 100.

The acute reference dose is calculated according to the following formula:

$$\text{ARfD (gen. pop.)} = \frac{\text{BMDL}_{10}}{\text{CAF}} = \frac{0.054 \text{ mg/kg bw}}{100} = 0.0005 \text{ mg/kg bw of propoxur}$$

This ARfD is considered protective of all populations including infants and children.

Determination of Acceptable Daily Intake (ADI)

To estimate dietary risk from repeat exposure for the general population, the BMDL₁₀ of 0.054 mg/kg bw for brain cholinesterase inhibition was selected from an acute oral comparative cholinesterase follow-up study in PND 11 rats. The quick acting and reversible nature of carbamates is considered as justification to default to the acute point of departure, which is typically lower than the subchronic or chronic LOAELs or NOAELs identified in carbamate dietary studies. In the case of propoxur, chronic daily exposure is considered to reflect a series of ongoing acute exposures, with each causing transient inhibition of cholinesterase.

Uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were used to derive the ADI. The *Pest Control Products Act* factor was reduced to 1-fold as discussed in the section on the *Pest Control Products Act* Hazard Characterization. Therefore, the CAF is 100.

The ADI is calculated according to the following formula:

$$\text{ADI (gen. pop.)} = \frac{\text{BMDL}_{10}}{\text{CAF}} = \frac{0.054 \text{ mg/kg bw}}{100} = 0.0005 \text{ mg/kg bw of propoxur}$$

This ADI is considered protective of all populations including infants and children.

Toxicology Endpoint Selection for Occupational and Residential Risk Assessment

Short- and Intermediate-Term Dermal Endpoints

A 13-week dermal study in rabbits is considered the most appropriate study for dermal risk assessments of all durations, since the effect of propoxur on cholinesterase levels is rapid and transient, suggesting that duration does not impact toxicity. No treatment-related effects were observed, including effects on cholinesterase activity, up to the limit dose of 1000 mg/kg bw/day (NOAEL = 1000 mg/kg bw/day). PND 11 pups were approximately 7 to 14-fold more sensitive than adults to BChE inhibition in the oral comparative cholinesterase assay. Since the dermal study was conducted in adults, there was uncertainty as to whether or not the sensitivity observed with oral exposure to the young would also be manifested via the dermal route. Additional uncertainty arises as to whether the fetus or nursing infant would also be more sensitive than adults as a result of an indirect exposure via the mother. The population (including workers) could include pregnant or lactating women whose offspring could potentially be exposed to an indirect dose of propoxur via their mother. Given the lack of appropriate dermal data to confirm or refute age sensitivity or data to assess the potential sensitivity of the fetus or nursing infant, an additional 10-fold uncertainty factor for database deficiency was applied to protect the young. The magnitude of this factor was considered appropriate based on the relative sensitivity of the young to brain cholinesterase inhibition, compared to adults, following direct oral exposure to propoxur. The target MOE is 1000 for the occupational risk assessment, accounting for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as the 10-fold uncertainty factor for database deficiency to address the potential sensitivity of the young. For residential risk assessment, the *Pest Control Products Act* factor was reduced to 1-fold for the reasons discussed in the *Pest Control Products Act* Hazard Characterization section.

Short- and Intermediate-Term Inhalation Endpoints

The NOAEL of 0.010 mg/L or 2.6 mg/kg bw/day from a 4-week inhalation toxicity study in rats was chosen for the short- and intermediate-term inhalation risk assessments. BChE inhibition occurred at the LOAEL of 0.047 mg/L, equivalent to 13 mg/kg bw/day. This LOAEL is consistent with another 4-week inhalation study where BChE inhibition occurred at 0.045 mg/L in female rats, as well as the 4-week interim measurement from a 12-week inhalation study that showed depressed EChE levels in female rats at 0.032 mg/L, or 8.6 mg/kg bw/day. The target MOE is 1000 for the occupational risk assessment, accounting for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as a 10-fold uncertainty factor for database deficiency to address the potential sensitivity of the young. For residential risk assessment, the *Pest Control Products Act* factor was reduced to 1-fold for the reasons discussed in the section on the *Pest Control Products Act* Hazard Characterization.

Non-dietary (Incidental) Oral Endpoint

For non-dietary (incidental) oral exposure (up to 6 months) of children, the selected toxicological endpoint (BMDL₁₀ of 0.54 mg/kg bw/day) is the same as for the ARfD and ADI determination. The *Pest Control Products Act* factor was reduced to 1-fold for the reasons discussed in the section on the *Pest Control Products Act* Hazard Characterization. Uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability result in a target MOE of 100. The selection of this study and MOE is considered protective of children exposed to propoxur by the oral route.

Toxicology Endpoint Selection for Aggregate Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential, and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). Acute, short-, and intermediate-term aggregate exposures to propoxur were assessed for dietary, drinking water, and residential (dermal and inhalation) exposures. The common endpoint of concern was BChE inhibition.

Endpoints selected for the aggregate assessment were the same as those selected for the route-specific assessments and did not differ on the basis of exposure duration. For the oral component, the BMDL₁₀ of 0.054 mg/kg bw was selected, based on an oral comparative cholinesterase assay in PND 11 rats. For the dermal component, the NOAEL of 1000 mg/kg bw/day from the 13-week dermal rabbit study was selected. For the inhalation component, the NOAEL of 0.010 mg/L, or 2.6 mg/kg bw/day from the 4-week rat inhalation study was selected. The target MOE is 100 for the oral component accounting for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The target MOE for the dermal and inhalation component is 1000, accounting for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as a 10-fold uncertainty factor for database deficiency to protect both the directly-exposed and indirectly-exposed young. The *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization section.

Cancer Potency Factor

For assessing oral cancer risk, the combined incidence rates of urinary bladder papillomas and/or carcinomas in male rats in a 2-year chronic oral toxicity study were used to generate a q_1^* of $3.7 \times 10^{-3} \text{ (mg/kg bw/day)}^{-1}$.

For assessing inhalation cancer risk, the combined incidences of hepatocellular adenomas and carcinomas were not available, thus only the incidences of hepatocellular adenomas in a chronic rat inhalation study were used to generate a q_1^* of $4.3 \times 10^{-2} \text{ (mg/kg bw/day)}^{-1}$.

Carcinogenic Endpoint Selection for Aggregate Assessment

Aggregate exposure to propoxur was assessed for dietary, drinking water, and residential (dermal and inhalation) exposure. Urinary bladder papillomas and carcinomas were seen by both the oral and inhalation route in rats. The q_1^* of $3.7 \times 10^{-3} \text{ (mg/kg bw/day)}^{-1}$ for urinary bladder papillomas resulting from exposure by the oral route in male rats is considered to be protective of all neoplasia produced by all routes of exposure.

Table 1 Toxicity Profile of Propoxur

Study/ Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL or BMDL [mg/kg bw (/day)]	Results/Effects
Neurotoxicity			
Acute Oral Comparative Cholinesterase Assay (CCA)	Adults: 0 (corn oil), 1, 2, 3, 5, or 10 mg/kg bw.	BMDL ₁₀ = 0.5 mg/kg bw for adult ♀ (↓BChE)	Adults ≥ 2.0 mg/kg bw: ↓ EChE and BChE
Sprague Dawley rats PND 11, adults 6/sex/dose	PND 11 pups: 0 (corn oil), 0.3, 0.5, 1.0, 2.0, or 3.0 mg/kg bw by gavage.		PND 11 pups ≥ 0.3 mg/kg bw: ↓ EChE and BChE
PMRA #2180505	EChE and BChE assessed approx. 5–10 min. post-dosing in adults, and 20–25 minutes for PND 11 pups Purity: 98.6%		Adults BMD ₂₀ (BMDL ₂₀) for EChE inhibition was 2.0(1.6) mg/kg bw (♂), and 1.3 (1.1) mg/kg bw (♀). BMD ₁₀ (BMDL ₁₀) for BChE was 1.1 (0.9) mg/kg bw (♂), and 0.6 (0.5) mg/kg bw (♀). PND 11 pups BMD ₂₀ (BMDL ₂₀) for EChE was 0.18(0.071) mg/kg bw (♂), and 0.11 (0.046) mg/kg bw (♀). BMD ₁₀ (BMDL ₁₀) for BChE was 0.082 (0.023) mg/kg bw.

Study/ Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL or BMDL [mg/kg bw (/day)]	Results/Effects
Acute Oral Cholinesterase Assay (follow-up) Sprague Dawley rats PND 11 11/sex/dose PMRA #2180506	PND 11 pups: 0 (corn oil), 0.1, 0.3 and 1.0 mg/kg bw by gavage. EChE and BChE assessed approx. 30 min. post-dosing Purity: 98.6%	BMDL ₁₀ = 0.054 for ↓ BChE (PND 11 ♀).	PND 11 pups ≥ 0.1 mg/kg bw: ↓ EChE (♀) 0.3 mg/kg bw: ↓ BChE; ↓ EChE (♂) The BMD ₂₀ (BMDL ₂₀) for EChE was 0.15 (0.075) mg/kg bw (♂), and 0.092 (0.047) mg/kg bw (♀). The BMD ₁₀ (BMDL ₁₀) for BChE was 0.13 (0.12) mg/kg bw (♂), and 0.071 (0.054) mg/kg bw (♀).
Acute oral cholinesterase assay (time course) Sprague Dawley rats Phase I (adults): 8 control or 6-9 treated ♂/timepoint Phase II (PND 11 pups): 3 control and 12 treated ♂ Phase III (PND 11 pups): 9 controls or 6-9 treated ♂/timepoint	Phase I: 0 (corn oil), or 5.0 mg/kg bw by gavage. Phases II and III: 0 (corn oil), or 3.0 mg/kg bw by gavage Phase II observed for overt toxicity. Phases I and III: EChE and BChE assessed 0.25 or 4 hours (controls) or 0.25, 0.5, 1, 2, or 4 hours (treated) post- dosing. Purity: 98.6%		PND 11 pups 3 mg/kg bw (♂): transient tremors, ↓ EChE and BChE (peak at 0.25 hours post-dosing, partial recovery to control levels by 4 hours post- dosing) Adults 3 mg/kg bw (♂): transient ↓ EChE and BChE (peak at 0.25 hours post- dosing, recovered to control levels by 4 hours post-dosing) Considered supplementary.

Table 2 Toxicological Endpoints for Use in Health Risk Assessment for Propoxur

Exposure Scenario	Dose	Endpoint	Study	CAF or Target MOE ^a
Acute Dietary, Chronic Dietary, or Non-Dietary Oral	BMDL ₁₀ = 0.054	Brain cholinesterase inhibition in PND 11 pups	Acute comparative cholinesterase assay in rats	100
	Acute Reference Dose = 0.0005 mg/kg bw Acceptable Daily Intake = 0.0005 mg/kg bw/day			
Short- or Intermediate- Term Dermal	NOAEL = 1000 mg/kg bw/day	No treatment-related effects, including no effects on cholinesterase.	13-week dermal toxicity study in rabbits	1000
Short- or Intermediate- Term Inhalation	NOAEL = 0.010 mg/L (2.6 mg/kg bw/day)	Brain cholinesterase inhibition at the LOAEL of 0.0467 mg/L, equivalent to 12.7 mg/kg bw/day.	4-week inhalation toxicity study in rats	1000
Aggregate, Combined ^b	Same route-specific endpoints and MOEs as specified above.			

Cancer (Oral, Aggregate, Combined ^b)	$q_1^* = 3.7 \times 10^{-3} \text{ (mg/kg bw/day)}^{-1}$ based on incidences of urinary bladder papillomas and/or carcinoma rates in male rats, in a 2-year oral carcinogenicity study
Cancer (Inhalation)	$q_1^* = 4.3 \times 10^{-2} \text{ (mg/kg bw/day)}^{-1}$ based on hepatocellular adenomas in male rats, in a 2-year inhalation carcinogenicity study

^a CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE (margin of exposure) refers to a target MOE for occupational and residential assessments

^b Aggregated for different exposure scenarios and combined for all routes of exposure (oral, dermal, inhalation).

Appendix III Revised Occupational and Residential Exposure Assessment

The PMRA received a pet collar transferable residue study and has revised the residential exposure risk assessment based on new toxicological endpoints, the 2012 United States Environmental Protection Agency (USEPA) Residential SOPs and the submitted pet collar transferable residue study. The study summary is included below. The revised assessment is presented in Tables 1, 5, 6, 9, 11, 14 and 16.

Pet Collar Transferable Residue Study

A pet collar transferable residue study was voluntarily submitted to the PMRA by the registrant. This study (Welch, 2011) was used in the PMRA's revised residential risk assessment to assess postapplication exposure to pet collars.

This study was designed to collect data to calculate transferable residues for propoxur on pet fur after application of an impregnated pet collar. Transferable residues were sampled using a mannequin hand wearing 5 layers of gloves to pet a dog after application of the collar. The application method, frequency, and monitoring times were relevant to the use pattern.

The quality of this study was considered acceptable for risk assessment purposes because the application methods were relevant to the registered Canadian use pattern. The estimates of transferable pet fur residues from this study were used to revise the pet collar risk assessment.

Fifteen dogs were sampled at each monitoring time. The method for collecting the residues accounts for transfer coefficients and exposure time. Therefore, the residues represent daily exposure to dogs wearing pet collars containing propoxur. The average Day 0 exposure (4 hrs after application of the pet collars) was 1.622 mg/day and the predicted 30 day average exposure was 0.248 mg/day.

Total deposition was not measured, which was a major study limitation; therefore, a comparison cannot be made between total deposition and transferable residue. There is no guideline for this type of study, and it is unknown if a mannequin hand is representative of a human hand when petting an animal. The study was well conducted; however, as it modelled only one activity (petting), it may not be representative of actual human contact with pets.

For pet collar applications the default transfer coefficients from the 2012 USEPA Residential SOPs were not used in conjunction with the residue data since, as noted above the method used to collect residues accounted for the transfer coefficient and exposure time.

Table 1 Summary of Use Scenarios and Risks of Concern

Use Scenario	Non-Cancer Risk Assessment			Cancer Risk Assessment		
	Inhalation	Dermal	Incidental Oral ^c	Inhalation	Dermal	Incidental Oral ^c
Commercial MLA ^a	Risks not of concern, except for mechanically-pressurized handgun ^b	Risks not of concern, except for mechanically-pressurized handgun ^b	Not required	Risks not of concern, except for mechanically-pressurized handgun ^b	Risks not of concern, except for mechanically-pressurized handgun ^b	Not required
Commercial Indoor Postapplication	Risks not of concern	Risks not of concern	Not required	Risks not of concern	Risks not of concern	Not required
Commercial Outdoor Postapplication ^f	Not required	Not required	Not required	Not required	Not required	Not required
Residential Applicator	Risks not of concern	Risks not of concern	Not required	Risks not of concern	Risks not of concern	Not required
Residential Indoor Postapplication	Risks of concern for children.	Risk not of concern	Risks of concern	Risks of concern.	Risks of concern.	Risks not of concern
Residential Outdoor Postapplication ^f	Not required	Not required	Not required	Not required	Not required	Not required
Bait Tray Applicator and Postapplication ^f	Not required	Not required	Not required	Not required	Not required	Not required
Residential Pet Collar Postapplication ^d	Not required	Risks not of concern	Risks of concern	Not required	Risks not of concern	Risks not of concern

^a MLA = mixer, loader, applicator.^b Target MOEs were not met for mechanically-pressurized handgun.^c Incidental oral non-cancer risk assessments not required for commercial and MLA scenarios because children will not be in those situations.^d Inhalation risk assessments were not required for pet collars because inhalation exposure to propoxur from pet collars is considered to be negligible.^e Incidental oral cancer risk assessments are not required for commercial and MLA scenarios because children will not be in those situations.^f Inhalation risk assessments are not required for outdoor exposure because inhalation exposure to is considered to be negligible. Dermal and incidental oral risk assessments were not required for outdoor exposure because outdoor residential crack and crevice, spot, structural, and stinging insect nest treatments are limited to areas not frequented by, or inaccessible to, children and the potential for postapplication exposure is minimal. Bait tray applicator and postapplication exposure was considered to be negligible because the active ingredient is enclosed in a self-contained unit and is not available for exposure.

Table 2 Short-term Occupational Mixer, Loader, Applicator Dermal and Inhalation Exposure Estimates and Margins of Exposure

Site	Formulation ^a	Application Equipment ^b	PPE ^c	Application Rate ^d	ATPD (L/day) ^e	Dermal exposure (mg/kg bw/day) ^f	Dermal MOE ^g	Inhalation exposure (mg/kg bw/day) ^h	Inhalation MOE ⁱ	Combined MOE ^j
Indoors, outdoors, stinging insect nests, commercial, industrial and institutional locations	EC, SN (1% a.i.)	Manually-Pressurized Handwand	Baseline	0.0117 kg a.i./L	150	0.02	48320	9.92E-04	2622	2487
		Mechanically-Pressurized Handgun ^k	Baseline		3800	3.10	322	8.39E-02	31	28
			+ Respirator		3800	3.10	322	8.39E-03	310	158
			Mid-level		3800	1.36	733	8.39E-02	31	30
			+ Respirator		3800	1.36	733	8.39E-03	310	218
			Maximum		3800	1.02	985	8.39E-02	31	30
			+ Respirator		3800	1.02	985	8.39E-03	310	236
			Baseline		100	0.08	12242	2.21E-03	1177	1074
			+ Respirator		600	0.49	2040	1.33E-03	1962	1000
		Backpack	Baseline		150	0.12	8370	1.36E-03	1909	1554
		Paintbrush	Baseline		20	0.15	6518	2.17E-03	1196	1010
Stinging insect nests, boats, buses, ships, trains	PP (2% a.i.)	Aerosol	Baseline	0.011 kg a.i./can	3 cans/day	0.06	16537	6.79E-04	3829	3109

^a EC = emulsifiable concentrate, SN = solution, PP = pressurized product.

^b Mix, load and apply were assessed for manually-pressurized handwands and mechanically-pressurized handguns, backpack and paintbrush, and only application was assessed for aerosol.

^c Personal Protective Equipment (PPE); Baseline = long-sleeved shirt, long pants and chemical-resistant gloves, Mid-level = coveralls over long-sleeved shirt, long pants and chemical-resistant gloves, Maximum = chemical-resistant coveralls over long-sleeved shirt, long pants and chemical-resistant gloves, + Respirator = previous level of PPE with the addition of a respirator.

^d An application rate was provided only for the EC formulation. Since the solution formulation has the same percent guarantee as the mixed EC formulation this rate was used for both formulations. No rate was provided for aerosol formulations. The percent guarantee was used along with the can size to determine a rate in kg a.i./can.

^e ATPD = Area Treated per Day (L/day unless otherwise stated). Aerosol based on 0.5 container/day/house and a commercial applicator being able to treat 6 houses. Paintbrush based on 4 L/day/house and a commercial applicator being able to treat 5 houses.

^f Where dermal exposure (mg/kg bw/day) = (unit exposure × 0.001 mg/μg × area treated per day × application rate × dermal absorption)/80 kg. Dermal absorption not required because the dermal NOAEL is based on a dermal toxicity study.

^g MOE = margin of exposure; Dermal MOE = dermal NOAEL/dermal exposure, based on a short-, intermediate-term dermal NOAEL of 1000 mg/kg bw/day and a target MOE of 1000. Shaded cells indicate MOEs that are less than the target MOE.

^h Where inhalation exposure (mg/kg bw/day) = (unit exposure × 0.001 mg/μg × area treated per day × application rate)/80 kg. Inhalation exposure was also calculated using a protection factor of 90% for use of a respirator. Assumes 100% absorption through inhalation.

ⁱ MOE = margin of exposure; Inhalation MOE = inhalation NOAEL/inhalation exposure, based on a short-, intermediate-term inhalation NOAEL of 2.6 mg/kg bw/day and a target MOE of 1000. Shaded cells indicate MOEs that are less than the target MOE.

^j Dermal and inhalation exposure routes have the same adverse toxicological endpoint and target MOE. The MOEs were combined using the following equation. Combined MOE = 1/(1/MOE_{dermal} + 1/MOE_{inhalation}). Shaded cells indicate MOEs that are less than the target MOE.

^k The limitation on the amount handled per day to reach the target MOE is not practical for this application equipment.

Table 3 Dermal Exposure and Cancer Risk Estimates for Commercial Mixer, Loader, Applicators

Site	Formulation ^a	Application Equipment ^b	PPE ^c	Application Rate ^d	ATPD (L/day) ^e	ADD (mg/kg bw/day) ^f	LADD (mg/kg bw/day) ^g	Dermal Cancer Risk ^h	Combined Inhalation and Dermal Cancer Risk ⁱ	
									Without Respirator	With Respirator
Indoors, outdoors, stinging insect nests, commercial, industrial and institutional locations	EC, SN (1% a.i.)	Manually-Pressurized Handwand	Baseline	0.0117 kg a.i./L	150	4.14E-03	6.98E-05	3E-07	3E-07	
		Mechanically-Pressurized Handgun	Baseline		3800	0.62	1.05E-02	4E-05	4E-05	4E-05
			Mid-level		3800	0.27	4.60E-03	2E-05	2E-05	2E-05
			Maximum		3800	0.20	3.42E-03	1E-05	2E-05	1E-05
		Backpack	Baseline		150	0.02	4.19E-04	1E-06	2E-06	
		Paintbrush	Baseline		20	0.03	5.17E-04	2E-06	2E-06	
Stinging insect nests, boats, buses, ships, trains	PP (2% a.i.)	Aerosol	Baseline	0.011 kg a.i./can	3 cans/day	0.01	2.04E-04	8E-07	8E-07	

^a EC = emulsifiable concentrate, SN = solution, PP = pressurized product.

^b Mix, load and apply were assessed for mechanically-pressurized handguns and manually-pressurized handwands, backpack and paintbrush, and only application was assessed for aerosol.

^c PPE = Personal protective equipment. Baseline = long-sleeved shirt, long pants and chemical-resistant gloves, Mid-level = coveralls over long-sleeved shirt, long pants and chemical-resistant gloves, Maximum = chemical-resistant coveralls over long-sleeved shirt, long pants and chemical-resistant gloves.

^d An application rate was provided only for the EC formulation. Since the solution formulation has the same percent guarantee as the mixed EC formulation this rate was used for both formulations. No rate was provided for aerosol formulations. The percent guarantee was used along with the can size to determine a rate in kg.a.i./can. Aerosol formulation application rates are in kg a.i./can.

^e ATPD = area treated per day. Aerosol based on 0.5 container/day/house and a commercial applicator being able to treat 6 houses.

^f Where absorbed daily dose (ADD) = dermal exposure, as determined by PHED scenarios. Dermal Exposure = (Unit Exposure × Application rate × ATPD × DA)/80 kg. Dermal absorption (DA) factor of 20% applied.

^g Where lifetime average daily dose (LADD) = (ADD × treatment frequency × working duration)/(365 days × 78 years). Treatment frequency = 30 days/year for commercial applicators. Working duration = 16 years.

^h A q_1^* value of $0.0037 \text{ (mg/kg bw/day)}^{-1}$ was considered appropriate to use in the dermal cancer risk assessment. Shaded cells indicate cancer risks that are more than 1×10^{-5} . Cancer risks equal to or below 1×10^{-5} were considered to be acceptable.

ⁱ The LADD for both inhalation and dermal exposure were added and then multiplied by the q_1^* value of $0.0037 \text{ (mg/kg/day)}^{-1}$ to obtain combined dermal and inhalation cancer risks. Shaded cells indicate cancer risks that are more than 1×10^{-5} . Cancer risks with a respirator were not calculated if the risk without a respirator was below 1×10^{-5} . The inhalation LADDs used to calculate combined cancer risk can be found in Table 4.

Table 4 Inhalation Exposure and Cancer Risk Estimates for Occupational Mixer, Loader, Applicators

Site	Formulation ^a	Application Equipment ^b	PPE ^c	Application Rate ^d	ATPD (L/day) ^e	ADD (mg/kg bw/day) ^f	LADD (mg/kg bw/day) ^g	Cancer Risk ^h
Indoors, outdoors, stinging insect nests, commercial, industrial and institutional locations	EC, SN (1% a.i.)	Manually-Pressurized Handwand	No respirator	0.0117 kg a.i./L	150	9.92E-04	1.74E-05	6E-08
		Mechanically-Pressurized Handgun	No respirator		3800	8.39E-02	1.47E-03	5E-06
			Respirator		3800	8.39E-03	1.47E-04	5E-07
		Backpack	No respirator		150	1.36E-03	2.39E-05	8E-08
		Paintbrush	No respirator		20	2.17E-03	3.80E-05	1E-07
Stinging insect nests, boats, buses, ships, trains	PP (2% a.i.)	Aerosol	No respirator	0.011 kg a.i./can	3 cans/day	6.79E-04	1.19E-05	4E-08

^a EC = emulsifiable concentrate, SN = solution, PP = pressurized product.

^b Mix, load and apply were assessed for mechanically-pressurized handgun and manually-pressurized handwand, backpack and paintbrush, and only application was assessed for aerosol.

^c PPE = personal protective equipment.

^d An application rate was provided only for the EC formulation. Since the solution formulation has the same percent guarantee as the mixed EC formulation this rate was used for both formulations. No rate was provided for aerosol formulations. The percent guarantee was used along with the can size to determine a rate in g a.i./can. Aerosol formulation application rates are in g a.i./can.

^e ATPD = area treated per day. Aerosol based on 0.5 container/day/house and a commercial applicator being able to treat 6 houses.

^f Where absorbed daily dose (ADD) mg/kg bw/day = inhalation exposure, as determined by PHED scenarios. Inhalation exposure (mg/kg bw/day) = (unit exposure × area treated per day × application rate)/(80 kg × 1000 µg/mg). Inhalation exposure was also calculated using a protection factor of 90% for use of a respirator. Assumes 100% absorption through inhalation. Inhalation exposure values from Table 2.

^g Where lifetime average daily dose (LADD) = (ADD × treatment frequency × working duration)/(365 days × 78 years). Treatment frequency = 30 days/year for commercial applicators. Working duration = 16 years.

^h A q_1^* value of 0.043 (mg/kg bw/day)⁻¹ was considered appropriate to use in the cancer risk assessment. Cancer risks equal to or below 1×10^{-5} were considered to be acceptable.

Table 5 Short-term Residential Applicator Dermal and Inhalation Exposure Estimates and Margins of Exposure

Site	Formulation ^a	Application Equipment ^b	Application Rate ^c	Amount Handled ^d	Dermal Exposure (mg/kg bw/day) ^e	Inhalation Exposure (mg/kg bw/day) ^e	Dermal MOE ^g	Inhalation MOE ^g	Combined MOE ^h
Indoors, Outdoors	SN	Manually-Pressurized Handwand	0.0168 kg a.i./L	1.89 L	0.0604	9.64E-04	16563	2696	2318
	PP	Aerosol	4.28E-03 kg a.i./can	0.5 can	0.0231	1.11E-04	43247	23336	15157
	PA	Bait Trays	0.024 g/m ²	Negligible					
Pets	SR	Collar	4.27E-03 kg a.i./pet	2 pets	0.0282	Negligible	35443	Negligible	NA

^a SN = solution, PP = pressurized product, PA = paste, SR = slow release.

^b Aerosol dermal and inhalation units of exposure were obtained from a submitted mixer/loader/applicator exposure study (Knarr, 1991), mechanically-pressurized handwand, and pet collar unit exposures are from the USEPA Residential SOPs (2012).

^c Based on percent guarantee and density or weight of product.

^d Amount handled = per day; based on USEPA Residential SOPs (2012).

^e Where dermal exposure (mg/kg/day) = (unit exposure × Application Rate (AR) × Amount Handled per day)/80 kg. Dermal absorption not required because the dermal NOAEL is based on a dermal toxicity study.

^f Where inhalation exposure (mg/kg bw/day) = (unit exposure × AR × Amount Handled per day)/80 kg. Assumes no respirator is worn and 100% absorption through inhalation.

^g MOE = margin of exposure; MOE = NOAEL/Exposure, based on a short-, intermediate-term inhalation NOAEL of 2.6 mg/kg bw/day and a target MOE of 1000 and a short-, intermediate-term dermal NOAEL of 1000 mg/kg bw/day and a target MOE of 1000.

^h Dermal and inhalation exposure routes have the same adverse toxicological endpoint and target MOE. The MOEs were combined using the following equation. Combined MOE = 1/(1/MOE dermal + 1/MOE inhalation). NA = Not applicable.

Table 6 Dermal Exposure and Cancer Risk Estimates for Residential Applicators

Site	Formulation ^a	Application Equipment ^b	Application Rate ^c	Treatment Frequency ^d	ADD ^e (mg/kg bw/day)	LADD ^f (mg/kg bw/day)	Cancer Risk ^g	Combined Dermal and Inhalation Cancer Risk ^h
Indoors, Outdoors	SN	Manually-Pressurized Handwand	0.0168 kg a.i./L	2	1.21E-02	5.34E-05	2E-07	2E-07
	PP	Aerosol	4.28E-03 kg a.i./can	2	4.62E-03	2.05E-05	8E-08	8E-08
	PA	Bait Trays	0.024 g/m ²		Negligible			
Pets	SR	Pet Collar	4.27E-03 kg a.i./pet	2	5.64E-03	1.39E-05	5E-08	NA

^a SN = solution, PP = pressurized product, PA = paste, SR = slow release.

^b Aerosol dermal unit exposure values were obtained from a submitted mixer/loader/applicator exposure study (Knarr, 1991), manually-pressurized handwand, and pet collar dermal unit exposures are from the USEPA Residential SOPs (2012).

^c Based on percent guarantee and density or weight of product.

^d Based on the ORETF Use and Usage Survey (Johnson et al., 1999). For pet collars an average of 2 exposure days per year was assumed based on professional judgment.

^e Where absorbed daily dose (ADD) mg/kg bw/day = dermal exposure, as determined by the USEPA Residential SOPs (2012), and a submitted study (Knarr, 1991).

ADD = (application rate × unit exposure × amount handled × dermal absorption) / (body weight (80 kg) × 1000 µg/mg). Dermal absorption factor of 20% applied.

^f Where lifetime average daily dose (LADD) = (ADD × Treatment Frequency × exposure duration)/(365 days × 78 years). Exposure duration = 63 years. For pet collars exposure duration = 35 years.

^g A q₁* value of 0.0037 (mg/kg bw/day)⁻¹ was considered appropriate to use in the dermal cancer risk assessment. Cancer risks equal to or below 1 × 10⁻⁶ were considered to be acceptable.

^h The LADD for both inhalation and dermal exposure were added and a q₁* value of 0.0037 (mg/kg bw/day)⁻¹ was used to obtain combined dermal and inhalation cancer risks. The inhalation LADDs used to calculate combined cancer risk can be found in Table 7. Cancer risks equal to or below 1 × 10⁻⁶ were considered to be acceptable. NA = Not applicable.

Table 7 Inhalation Exposure and Cancer Risk Estimates for Residential Applicators

Site	Formulation ^a	Application Equipment ^b	Application Rate ^c	Treatment Frequency ^d	ADD ^e (mg/kg bw/day)	LADD ^f (mg/kg bw/day)	Cancer Risk ^g
Indoors, Outdoors	SN	Manually-Pressurized Handwand	0.0168 kg a.i./L	2	9.64E-06	4.27E-06	2E-07
	PP	Aerosol	4.28E-03 kg a.i./can	2	1.11E-04	4.93E-07	2E-08
	PA	Bait Trays	0.024 g/m ²	Negligible			
Indoors	SR	Pet Collar	4.27E-03 kg a.i./pet	2	Negligible		

^a SN = solution, PP = pressurized product., PA = Paste, SR = slow release.

^b Aerosol inhalation unit exposure were obtained from a submitted mixer/loader/applicator exposure study (Knarr, 1991), manually-pressurized handwand inhalation unit exposures are from the USEPA Residential SOPs (2012).

^c Based on percent guarantee and density or weight of product.

^d Based on the ORETF Use and Usage Survey (Johnson et al., 1999) and professional judgment.

^e Where absorbed daily dose (ADD) mg/kg bw/day = inhalation exposure, as determined by the USEPA Residential SOPs (2012) and a submitted study (Knarr, 1991).

ADD = (application rate × unit exposure × amount handled) / (body weight (80 kg) × 1000 µg/mg). Assumes 100% absorption through inhalation. Inhalation exposure values from Table 5.

^f Lifetime Average Daily Dose (LADD) = ADD × Treatment Frequency × exposure duration/(365 days × 78 years). Exposure duration = 63 years, for manually-pressurized handwand and aerosols.

^g A q₁* value of 0.043 (mg/kg bw/day)⁻¹ was considered appropriate to use in the cancer risk assessment. Cancer risks equal to or below 1 × 10⁻⁶ were considered to be acceptable.

Table 8 Postapplication Dermal Exposure Estimates and MOEs from Indoor Application

Exposure Scenario	Life Stage	Transferable Residue (µg/cm ²) ^a	Exposure Time (hr/day)	Dermal Dose (mg/kg bw/day) ^b	MOE ^c	Combined Dermal & Inhalation MOE ^d	Dermal, Inhalation & Incidental Oral ARI ^e
Perimeter/Spot (coarse)	Carpet	Adults	0.27	8	0.184	5447	NA
		Youth	0.27	5	0.133	7540	NA
		Children	0.27	4	0.177	5658	NA
	Hard Surface	Adults	0.36	2	0.0612	16340	3108
		Youth	0.36	1	0.0354	28274	2530
		Children	0.36	2	0.118	8488	NA
Perimeter/Spot (pin-stream)	Carpet	Adults	0.066	8	0.0449	22282	3274
		Youth	0.066	5	0.0324	30844	2712
		Children	0.066	4	0.0432	23148	NA
	Hard Surface	Adults	0.088	2	0.0150	66845	3630
		Youth	0.088	1	0.00865	115666	2712
		Children	0.088	2	0.0288	34722	NA

Exposure Scenario		Life Stage	Transferable Residue ($\mu\text{g}/\text{cm}^2$) ^a	Exposure Time (hr/day)	Dermal Dose (mg/kg bw/day) ^b	MOE ^c	Combined Dermal & Inhalation MOE ^d	Dermal, Inhalation & Incidental Oral ARI ^e
Crack and Crevice	Carpet	Adults	0.018	8	0.0122	81699	3666	NA
		Youth	0.018	5	0.00884	113095	2779	NA
		Children	0.018	4	0.0118	84877	NA	0.227
	Hard Surface	Adults	0.024	2	0.00408	245098	3779	NA
		Youth	0.024	1	0.00236	424107	2760	NA
		Children	0.024	2	0.00785	127315	NA	0.450

^a Where Transferable Residue ($\mu\text{g}/\text{cm}^2$) = Residue ($\mu\text{g}/\text{cm}^2$) \times Fraction Transferred (%). Default residues from the USEPA Residential SOPs (2012) were used. For Perimeter (coarse), Perimeter (pin stream), and Crack & Crevice the following residue values were used 4.5, 1.10, and 0.30 $\mu\text{g}/\text{cm}^2$, respectively.

^b Where Dermal Dose (mg/kg bw/day) = (Transferable Residue ($\mu\text{g}/\text{cm}^2$) \times 0.001 mg/ μg \times Transfer Coefficient (cm^2/hr) \times Exposure Time (hr/day))/Body Weight (kg). Transfer coefficients of 6800, 5600, and 1800 were used for adults, youth and children respectively, body weights of 80, 57 and 11 kg were used for adults, youths, and children respectively, as stated in the USEPA Residential SOPs (2012). Dermal absorption not required because the dermal NOAEL is based on a dermal toxicity study.

^c MOE = margin of exposure; MOE = NOAEL/exposure, based on a short-/intermediate-term dermal NOAEL of 1000 mg/kg bw/day and a target MOE of 1000.

^d Dermal and inhalation exposure routes have the same adverse toxicological endpoint and target MOE. The MOEs were combined using the following equation. The inhalation MOEs used to calculate combined exposure can be found in Table 10. NA = Not applicable.

Combined MOE = $1/(1/\text{MOE}_{\text{dermal}} + 1/\text{MOE}_{\text{inhalation}})$.

^e Dermal, inhalation, and incidental oral exposure routes have the same adverse toxicological endpoint but different target MOEs. The MOEs were combined using the following equation.

Aggregate Risk Index (ARI) = $1/(1000/\text{MOE}_{\text{dermal}} + 1000/\text{MOE}_{\text{inhalation}} + 100/\text{MOE}_{\text{incidental oral}})$. ARIs great than one indicate no risk concerns. Shaded cells indicate ARIs that are less than 1. The incidental oral MOEs used to calculate combined exposure can be found in Table 11.

Table 9 Postapplication Dermal Exposure Estimates and MOEs from Pet Collar Application Using Chemical Specific Data

Formulation	Life Stage	Exposure (mg/day) ^a	Dermal Dose (mg/kg bw/day) ^b	MOE ^c	Dermal and Incidental Oral ARI ^d
Pet Collar (slow release)	Adults	1.622	2.03E-02	49322	NA
	Youth	1.622	2.85E-02	35142	NA
	Children	1.622	1.47E-02	6790	0.35

^a Exposure as determined in the review of Welch, 2011, based on the Day 0 average residue.

^b Where Dermal Dose (mg/kg bw/day) = (Exposure (mg/day)/Body Weight (kg)). Body weights for adults, youth, and children were 80, 57, and 11 kg, as stated in the USEPA Residential SOPs (2012). Dermal absorption not required because the dermal NOAEL is based on a dermal toxicity study.

^c MOE = margin of exposure; Dermal MOE = dermal NOAEL/dermal exposure, based on a short-/intermediate-term dermal NOAEL of 1000 mg/kg bw/day and a target MOE of 1000.

^d Dermal and incidental oral exposure routes have the same adverse toxicological endpoint but different target MOEs. The MOEs were combined using the following equation.

Aggregate Risk Index (ARI) = $1/(1000/\text{MOE}_{\text{dermal}} + 100/\text{MOE}_{\text{incidental oral}})$. ARIs great than one indicate no risk concerns. Shaded cells indicate ARIs less than one. NA = Not applicable.

Table 10 Postapplication Inhalation Exposure Estimates and MOEs from Indoor Surface Directed Application

Exposure Duration	Age category	Inhalation rates (m ³ /hr)	Mass of a.i. (mg)	Exposure Time (hr)	Body weight (kg)	Inhalation Exposure (mg/kg bw/day) ^a	MOE ^b
Short-, Intermediate-term	Adults	0.64	2138	16	80	6.77E-04	3839
	Youth	0.63	2138	16	57	9.36E-04	2778
	Children	0.33	2138	18	11	2.91E-03	894

$$^a \text{ Where inhalation exposure (mg/kg bw/day)} = \frac{IR \times M}{ACH \times V} \times \left[1 - \frac{(ACH \times e^{-k \times ET}) - (k \times e^{-ACH \times ET})}{ACH - k} \right] \times \frac{1}{BW}$$

The equation assumes 100% absorption through inhalation, air exchanges (ACH) = 0.45 hr⁻¹, volume of a room (V) = 33 m³, decay rate (k) = 4.27E-05 hr⁻¹, M = mass of a.i., ET = exposure time, IR = inhalation rates, BW = body weights. Inhalation rates and body weights as stated in the USEPA Residential SOPs (2012).

^b MOE = margin of exposure; Inhalation MOE = inhalation NOAEL/inhalation exposure, based on a short-/intermediate-term inhalation NOAEL of 2.6 mg/kg bw/day and a target MOE of 1000. Shaded cells indicate MOEs that did not reach the target MOE.

Table 11 Incidental Oral Exposure Estimates and MOEs for Hand-to-Mouth Transfer to Children

Scenario	Surface	Hand Residue Loading (mg/cm ²) ^a	Oral Dose (mg/kg bw/day) ^b	MOE ^c
Perimeter/Spot (coarse)	Carpet	9.72E-04	0.026	2
	Hard Surface	6.48E-04	0.009	6
Perimeter/Spot (pin-stream)	Carpet	2.38E-04	0.006	8
	Hard Surface	1.58E-04	0.002	25
Crack and Crevice	Carpet	6.48E-04	0.002	31
	Hard Surface	4.32E-04	0.0006	92
Pet Collar	Pet Fur	2.16E-04 ^d	1.47E-03 ^e	37 ^f

^a Based on the dermal exposure from indoor applications without the body weight from Table 8.

^b Where Absorbed Dose (mg/kg/day) = [Hand Residue (mg/cm²) × (Fraction of hand mouthed/event (0.13) × Surface Area of one hand (150 cm²)) × (Exposure Time (hr) × Replenishment Intervals (4/hr)) × (1 - (1 - Saliva Extraction Factor (0.48))^{Number events per hour (20)/Replenishment Intervals (4/hr)})] / Body Weight (11 kg). Exposure times for carpet and hard surfaces were 4 and 2 hrs, respectively, as stated in the USEPA Residential SOPs (2012).

^c MOE = margin of exposure; Oral MOE = oral BMDL₁₀/oral exposure, based on an oral BMDL₁₀ of 0.054 mg/kg bw/day and a target MOE of 100. Shaded cells indicate MOEs that are below the target MOE.

^d Based on the dermal exposure from pet collars without the body weight and dermal absorption factor.

^e Where Absorbed Dose (mg/kg bw/day) = [Hand Residue (mg) × (Fraction of hand mouthed (0.13) × Surface Area Hand (150cm²)) × (Exposure Time (1 hr/day) × Replenishment Intervals (4/hr)) × (1 - (1 - Saliva Extraction (0.48))^{Number of hand-to-mouth events (20/hr)/Replenishment Interval (4/hr)})] / Body Weight (11 kg).

^f MOE = margin of exposure; Oral MOE = oral BMDL₁₀/oral exposure, based on an oral BMDL₁₀ of 0.054 mg/kg bw/day and a target MOE of 100.

Table 12 Incidental Oral Exposure Estimates and MOEs for Object-to-Mouth Transfer to Children

Scenario	Surface	Object Residue ($\mu\text{g}/\text{cm}^2$) ^a	Oral Dose ($\text{mg}/\text{kg bw}/\text{day}$) ^b	MOE ^c
Perimeter/Spot (coarse)	Carpet	0.27	3.53E-03	15
	Hard Surface	0.36	2.35E-03	23
Perimeter/Spot (pin-stream)	Carpet	0.066	8.63E-04	63
	Hard Surface	0.088	5.75E-04	94
Crack and Crevice	Carpet	0.018	2.35E-04	230
	Hard Surface	0.024	1.57E-04	344

^a Where Object Residue ($\mu\text{g}/\text{cm}^2$) = Residue Available for Transfer ($\mu\text{g}/\text{cm}^2$) \times Fraction of Residue Transferred. The default values for residue available for transfer for perimeter (coarse), perimeter (pin stream), and crack and crevice are 4.5, 1.1, and 0.30 $\mu\text{g}/\text{cm}^2$, respectively, and the fraction transferred for carpets and hard surfaces were 6% and 8%, respectively, as stated in the USEPA Residential SOPs (2012).

^b Where Absorbed Dose ($\text{mg}/\text{kg bw}/\text{day}$) = [Object Residue ($\mu\text{g}/\text{cm}^2$) \times 0.001 $\text{mg}/\mu\text{g}$ \times Surface Area Object Mouthed (10 cm^2/event) \times (Exposure Time (hr/day) \times Replenishment Intervals (4hr)) \times (1 - Saliva Extraction (0.48)) Number of object-to-mouth events (14/hr)/Replenishment Intervals (4hr)] / Body weight (11 kg). Exposure times for carpets and hard surfaces were 4 and 2 hrs/day, respectively, as stated in the USEPA Residential SOPs (2012).

^c MOE = margin of exposure; Oral MOE = oral BMDL₁₀/oral exposure, based on an oral BMDL₁₀ of 0.054 $\text{mg}/\text{kg bw}/\text{day}$ and a target MOE of 100. Shaded cells indicate MOEs that are below the target MOE.

Table 13 Dermal Exposure and Cancer Risk Estimates for Postapplication Residential Exposure to Indoor Surfaces

Exposure Scenario	Age Category	ADD ^a ($\text{mg}/\text{kg bw}/\text{day}$)	LADD ^b ($\text{mg}/\text{kg bw}/\text{day}$)	Dermal Cancer Risk ^{c,g}	Lifetime Dermal Cancer Risk ^{d,g}	Combined Dermal, Inhalation & Incidental Oral Cancer Risk ^{e,g}	Lifetime Cancer Risk ^{f,g}
Perimeter/Spot (Coarse)	Carpet	Adult	3.67E-02	2.44E-03	9.E-06	9.E-06	1E-05
		Youth	2.65E-02	1.40E-04	5.E-07	5.E-07	
		Child	3.53E-02	1.86E-04	7.E-07	7.E-07	
	Hard Surface	Adult	1.22E-02	8.13E-04	3.E-06	3.E-06	4E-06
		Youth	7.07E-03	3.73E-05	1.E-07	1.E-07	
		Child	2.36E-02	1.24E-04	5.E-07	5.E-07	
Perimeter/Spot (Pin Stream)	Carpet	Adult	8.98E-03	5.96E-04	2.E-06	2.E-06	2E-06
		Youth	6.48E-03	3.42E-05	1.E-07	1.E-07	
		Child	8.64E-03	4.55E-05	2.E-07	2.E-07	
	Hard Surface	Adult	2.99E-03	1.99E-04	7.E-07	7.E-07	9E-07
		Youth	1.73E-03	9.11E-06	3.E-08	3.E-08	
		Child	5.76E-03	3.03E-05	1.E-07	1.E-07	
Crack and Crevice	Carpet	Adult	2.45E-03	1.63E-04	6.E-07	6.E-07	7E-07
		Youth	1.77E-03	9.32E-06	3.E-08	3.E-08	
		Child	2.36E-03	1.24E-05	5.E-08	5.E-08	
	Hard Surface	Adult	8.16E-04	5.42E-05	2.E-07	2.E-07	2E-07
		Youth	4.72E-04	2.48E-06	9.E-09	9.E-09	
		Child	1.57E-03	8.28E-06	3.E-08	3.E-08	

^a Where absorbed daily dose (ADD) mg/kg bw/day = (Transferable Residue (µg/cm²) × 0.001 mg/µg × Transfer Coefficient (cm²/hr) × Exposure Time (hr/day) × Dermal Absorption (20%))/Body Weight. Transfer coefficients of 6800, 5600, and 1800 were used for adults, youth and children respectively, body weights of 80, 57 and 11 kg were used for adults, youths, and children respectively, as stated in the USEPA Residential SOPs (2012).

^b Where lifetime average daily dose (LADD) = (ADD × Exposure days/year × exposure duration)/(365 days × 78 years). Exposure duration = 63 years for adults and 5 years each for children and youths. 30 exposure days per year was based on professional judgment, and number of applications per year.

^c A q_1^* value of 0.0037 (mg/kg bw/day)⁻¹ was considered appropriate to use in the cancer risk assessment.

^d Where lifetime cancer risks = sum of cancer risks from adult, youth and child exposure.

^e The LADD for inhalation, dermal, and incidental oral (children) exposure were added and a q_1^* value of 0.0037 (mg/kg bw/day)⁻¹ was used to obtain combined dermal, inhalation, and incidental oral cancer risks. The inhalation LADDs used to calculate combined cancer risk can be found in Table 15. The incidental oral LADDs used to calculate combined cancer risk can be found in Table 16.

^f Where lifetime cancer risks = sum of cancer risks from adult, youth and child exposure.

^g Cancer risks equal to or below 1×10^{-6} were considered to be acceptable. Shaded cells indicate cancer risks that are more than 1×10^{-6} .

Table 14 Dermal Exposure and Cancer Risk Estimates for Postapplication Exposure to Pet Collars Using Chemical Specific Data

Formulation	Age Category	Exposure (mg/day) ^a	ADD (mg/kg bw/day) ^b	Exposure Days per Year ^c	LADD ^d (mg/kg bw/day)	Dermal Cancer Risk ^e	Lifetime Dermal Cancer Risk ^f	Combined Dermal and Incidental Oral LADD ^g	Lifetime Cancer Risk ^e
Pet Collar (slow release)	Adult	0.248	6.20E-04	180	1.37E-04	5.E-07	1.E-06	NA	NA
	Youth	0.248	8.70E-04	180	2.75E-05	1.E-07		NA	NA
	Child	0.248	4.51E-03	180	1.42E-04	5.E-07		1.50E-04	6E-07

^a Exposure as determine in the review of Welch, 2011, based on the 30 day time weighted average residue.

^b Where absorbed daily dose (ADD) mg/kg bw/day = dermal exposure = (Exposure (mg/day) × Dermal Absorption (20%))/Body Weight (kg). Body weights for adults, youth, and children were 80, 57, and 11 kg, as stated in the USEPA Residential SOPs (2012).

^c Postapplication exposure days/year based on professional judgement, number of applications per year, efficacy, and a maximum intermediate exposure of 6 months.

^d Lifetime Average Daily Dose (LADD) = ADD × Exposure days/year × exposure duration/(365 days × 78 years). Exposure duration = 35 years for adults and 5 years each for children and youths.

^e A q_1^* value of 0.0037 (mg/kg bw/day)⁻¹ was considered appropriate to use in the cancer risk assessment. Cancer risks equal to or below 1×10^{-6} were considered to be acceptable. NA = Not applicable.

^f Where cumulative lifetime cancer risks = sum of cancer risks from adult, youth and child exposure. Cancer risks equal to or below 1×10^{-6} were considered to be acceptable.

^g The LADD for dermal and incidental oral (children) exposure were added. The incidental oral LADDs used to calculate combined cancer risk can be found in Table 16.

Table 15 Inhalation Exposure and Cancer Risk Estimates for Indoor Residential Postapplication Exposure Following Surface Directed Application

Age Category	ADD (mg/kg bw/day) ^a	Exposure Days per Year ^b	LADD (mg/kg bw/day) ^c	Inhalation Cancer Risk ^d	Lifetime Cancer Risk ^e
Adult	6.77E-04	30	4.50E-05	2E-06	3E-06
Youth	9.36E-04	30	4.93E-06	2E-07	
Child	2.91E-03	30	1.53E-05	7E-07	

^a Where absorbed daily dose (ADD) mg/kg bw/day = inhalation exposure = $\frac{IR \times M}{ACH \times V} \times \left[1 - \frac{(ACH \times e^{-k \times ET}) - (k \times e^{-ACH \times ET})}{ACH - k} \right] \times \frac{1}{BW}$

The equation assumes 100% absorption through inhalation, air exchanges (ACH) = 1/hr, volume of a room (V) = 33 m³, decay rate (k) = 1/hr, M = mass of a.i., ET = exposure time. Inhalation rates (IR) of 0.64, 0.63 and 0.33 m³/hr and body weights (BW) of 80, 57 and 11 kg were used for adults, youth and children respectively, as stated in the USEPA Residential SOPs (2012). Inhalation exposure values from Table 10.

^b Postapplication exposure days/year based on professional judgment, number of applications per year, and minimum exposure time of 1 month.

^c Where lifetime average daily dose (LADD) = (ADD × Exposure days/year × exposure duration)/(365 days × 78 years). Exposure duration = 63 years for adults and 5 years each for children and youths.

^d A q_1^* value of 0.043 (mg/kg bw/day)⁻¹ was considered appropriate to use in the cancer risk assessment.

^e Where cumulative lifetime cancer risks = sum of cancer risks from child, youth and adult exposure. Cancer risks equal to or below 1×10^{-6} were considered to be acceptable.

Table 16 Incidental Oral Exposure and Cancer Risks for Hand-to-Mouth Transfer to Children

Exposure Scenario		ADD ^a (mg/kg bw/day)	Exposure Days/Year ^b	LADD ^c (mg/kg bw/day)	Cancer Risk ^d
Perimeter/Spot (Coarse)	Carpet	2.65E-02	30	1.40E-04	5.E-07
	Hard Surface	8.84E-03	30	4.66E-05	2.E-07
Perimeter/Spot (Pin stream)	Carpet	6.48E-03	30	3.42E-05	1.E-07
	Hard Surface	2.16E-03	30	1.14E-05	4.E-08
Crack and Crevice	Carpet	1.77E-03	30	9.32E-06	3.E-08
	Hard Surface	5.89E-04	30	3.11E-06	1.E-08
Pet Collar	Pet Fur	2.25E-04	180	7.13E-06	3.E-08

^a Where absorbed daily dose (ADD) mg/kg bw/day = oral exposure = [Hand Residue (mg/cm²) × (Fraction of hand mouthed/event (0.13) × Surface Area of one hand (150 cm²)) × (Exposure Time (hr) × Replenishment Intervals (4/hr)) × (1 - (1 - Saliva Extraction Factor (0.48))^{Number of hand-to-mouth events (14/hr)/Replenishment Intervals (4/hr)})] / Body Weight (11 kg). Exposure times for carpet, hard surfaces, and pet collars were 4, 2, and 1 hrs, respectively, as stated in the USEPA Residential SOPs (2012).

^b Postapplication exposure days/year based on professional judgment, number of applications per year, efficacy, and potential exposure duration (minimum 1 month, maximum 6 months).

^c Where lifetime average daily dose (LADD) = (ADD × Exposure days/year × exposure duration)/(365 days × 78 years). Exposure duration = 5 years for children.

^d A q_1^* value of 0.0037 (mg/kg bw/day)⁻¹ was considered appropriate to use in the cancer risk assessment. Cancer risks equal to or below 1×10^{-6} were considered to be acceptable.

Table 17 Incidental Oral Exposure and Cancer Risks for Object-to-Mouth Transfer to Children

Exposure Scenario		ADD ^a (mg/kg bw/day)	Exposure Days/Year ^b	LADD ^c (mg/kg bw/day)	Cancer Risk ^d
Perimeter/Spot (Coarse)	Carpet	3.53E-03	30	1.86E-05	7.E-08
	Hard Surface	2.35E-03	30	1.24E-05	5.E-08
Perimeter/Spot (Pin stream)	Carpet	8.63E-04	30	4.55E-06	2.E-08
	Hard Surface	5.75E-04	30	3.03E-06	1.E-08
Crack and Crevice	Carpet	2.35E-04	30	1.24E-06	5.E-09
	Hard Surface	1.57E-04	30	8.26E-07	3.E-09

^a Where absorbed daily dose (ADD) mg/kg bw/day = oral exposure = Object Residue (μg/cm²) × 0.001 mg/μg × Surface Area Object Mouthed (10 cm²/event) × (Exposure Time (hr/day) × Replenishment Intervals (4/hr)) × (1 - (1 - Saliva Extraction (0.48))^{Number of object-to-mouth events (14/hr)/Replenishment Intervals (4/hr)})] / Body weight (11 kg). Exposure times for carpets and hard surfaces were 4 and 2 hrs/day, respectively, as stated in the USEPA Residential SOPs (2012).

^b Postapplication exposure days/year based on professional judgment.

^c Where lifetime average daily dose (LADD) = (ADD × Exposure days/year × exposure duration)/(365 days × 78 years). Exposure duration = 5 years for children.

^d A q_1^* value of 0.0037 (mg/kg bw/day)⁻¹ was considered appropriate to use in the cancer risk assessment. Cancer risks equal to or below 1×10^{-6} were considered to be acceptable.

Appendix IV Revised Dietary Exposure Assessment

As a result of revisions to the acute and chronic reference doses (see Appendix II, Table 2), the dietary exposure and risk assessment for propoxur was updated to incorporate the revised reference doses (i.e. ARfD and ADI). All other dietary inputs used in PRVD2011-09 were unchanged.

Table 1 Dietary Exposure and Risk Estimates for Propoxur

Population Subgroup	Acute Dietary Exposure Risk		Chronic Dietary Exposure Risk		Cancer Dietary Exposure Risk	
	Exposure ¹ (mg/kg bw/day) 95 th Percentile	% ARfD	Exposure ² (mg/kg bw/day)	% ADI	Exposure ³ (mg/kg bw/day) ⁻¹	Lifetime Risk
Food-only*						
Canadian Population	0.000155	31	0.000047	9.4	0.000055	2E-07
All Infants (< 1 year old)	0.000239	48	0.000080	16	N/A	N/A
Children 1–2 years old	0.000359	72	0.000167	33		
Children 3–5 years old	0.000265	53	0.000124	25		
Children 6–12 years old	0.000167	33	0.000075	15		
Youth 13–19 years old	0.000108	22	0.000042	8.3		
Adults 20–49 years old	0.000080	16	0.000033	6.6		
Adults 50+ years old	0.000078	16	0.000032	6.4		
Females 13–49 years old	0.000082	16	0.000032	6.5		
Toxicological Reference Doses						
¹ Acute Reference Dose (ARfD) = 0.0005 mg/kg bw						
² Acceptable Daily Intake (ADI) = 0.0005 mg/kg bw/day						
³ Cancer Potency Factor (q_1^*) = 3.7×10^{-3} (mg/kg bw/day) ⁻¹						

* Highest residue detected in CFIA monitoring database (2002-2008) for domestic products with the inclusion of residues detected in imported commodities, and assuming all food handling establishments in Canada use propoxur.

Appendix V Label Amendments for Products Containing Propoxur

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Additional information on labels of currently registered products should not be removed unless it contradicts the label statements below.

A submission to request label revisions will be required within 90 days of publication of this re-evaluation decision document.

The following uses were not supported and directions for these uses must be **removed** from labels:

- Outdoor application for blackflies, gnats, mosquitoes, punkies; and
- Commercial, industrial and institutional locations for punkies and sandflies.

Registration of the following uses has been cancelled and directions for these uses must be **removed** from labels:

- All pet collar, indoor domestic-class products (except bait trays), and application of commercial-class products in indoor residential areas.

The labels of end-use products for all other uses in Canada are to be amended by including the following statements intended to further protect workers, consumers, bystanders, and the environment.

1.1 Label Amendments based on Toxicology

The technical product must include the following statement:

“Caution – Eye irritant”

1.1.1 Use Standards for Commercial Class Products Containing Propoxur

Labels of pesticide products must carry statements regarding symptoms of poisoning and treatment, which are especially important for those who may be overexposed when working with the product in a commercial or industrial setting (for example, mixers/loaders who handle more concentrated forms). Based on the toxicological assessments, the label text of the propoxur-containing products should be expanded and/or standardized, as follows:

“Toxicological Information: Propoxur is a carbamate which is a cholinesterase inhibitor. Typical symptoms of overexposure to cholinesterase inhibitors include malaise, muscle weakness, dizziness and sweating. Headache, salivation, nausea, vomiting, abdominal pain and diarrhea are often prominent. A life-threatening poisoning is signified by loss of consciousness, incontinence, convulsions and respiratory depression with a secondary cardiovascular component. Treat symptomatically. If exposed, plasma and red blood cell cholinesterase tests may indicate degree of exposure (baseline data are useful). However, if a blood sample is taken several hours after

exposure, it is unlikely that blood cholinesterase activities will be depressed, due to rapid reactivation of cholinesterase. Atropine, only by injection, is the preferable antidote. Do not use pralidoxime. In cases of severe acute poisoning, use antidotes immediately after establishing an open airway and respiration. With oral exposure, the decision of whether to induce vomiting or not should be made by an attending physician.”

1.1.2 Use Standards for Domestic-Class Products Containing Propoxur

“Toxicological Information – All Formulations: This product contains a pesticide that is a cholinesterase inhibitor (anti-cholinesterase compound). Symptoms of human poisoning may include headache, weakness, sweating, blurred vision, nausea and diarrhea. Obtain medical attention or call a poison control centre at once. Atropine is antidotal.”

1.2 Uses Requiring Mitigation

Mitigation measures are required for indoor commercial-class products and outdoor commercial-class and domestic-class products to reduce the risk of residential postapplication exposure.

1.2.1 Use Precautions

Additional label statements for commercial application (i.e. commercial-class labels) are required regarding use precautions.

- Application of propoxur indoors must be limited to non-residential locations where children cannot be exposed, such as industrial buildings and storage areas.
- Application of propoxur outdoors must be limited to crack and crevice, structural and stinging insect nest treatments and must not be applied to vegetation, plants, grass and/or any area accessible to children.
- Directions for application by aircraft must be removed.

The following statements must be added to DIRECTIONS FOR USE:

For all formulations:

“DO NOT use on indoor residential use sites, including homes, schools, hospitals, public buildings, day care facilities, motels, hotels, passenger areas of trains, buses or airplanes, and other indoor locations where children may be exposed.”

“Outdoor application is limited to crack and crevice, structural, and stinging insect nest treatments and the product must not be applied to vegetation, plants, grass and/or any area accessible to children.”

For aerosol formulations:

“DO NOT use as a space spray.”

For liquid formulations:

“DO NOT use mechanically-pressurized equipment.”

“DO NOT apply as a broadcast application. Application is limited to perimeter (one foot of wall and floor space treated around perimeter) and crack and crevice (aerosol application using a pin stream nozzle into cracks and crevices) application.”

Additional label statements for domestic-class products (except bait trays) are required regarding use precautions. All directions for indoor use must be removed from the labels and statements must be added to include the following directions:

“For outdoor use only. DO NOT use indoors.”

“DO NOT spray on animals.”

“Outdoor application is limited to crack and crevice, structural, and stinging insect nest treatments and must not be applied to vegetation, plants, grass and/or any area accessible to children.”

1.2.2 Personal Protective Equipment

Additional label statements for commercial application (i.e. commercial-class labels) are required regarding personal protective equipment. Statements must be added to include the following directions:

“Wear long pants, long-sleeved shirt, chemical-resistant footwear, and chemical-resistant gloves when mixing, loading and applying propoxur. Pants must be worn outside footwear to prevent pooling within boots.”

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A. List of Studies/Information Submitted by Registrant – Unpublished

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